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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/688,780	10/15/2003	Robert Pawliuk	IOI-024	9532

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BOSTON, MA 02109

EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 03/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/688,780	PAWLIUK ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2005*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-2, 4-21* is/are pending in the application.

4a) Of the above claim(s) *3-13 and 17-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4 and 14-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 12/01/05 has been acknowledged.

Claims 1-20 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is ***571-273-8300.***

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-2, 4, 14-16), wherein the elected species are HIV and IL-1Ra in the reply filed on 12/01/05 is acknowledged.

Claims 5-13 and 17-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 12/01/05.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for a method for treating arthritis by administering an intra-articular injection of a lentiviral vector encoding interleukin-1 receptor antagonist (IL-1Ra), does not reasonably provide enablement for a method for treating arthritis by delivering to a subject a lentiviral gene delivery vector encoding any other therapeutic gene via any and all routes of administration. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to use the invention commensurate in scope with these claims.

Nature Of Invention

The instant invention relates to a method for the treatment of arthritis via gene therapy

Breadth Of Claims And Guidance Provided in the Specification

The scope of the invention as claimed encompasses a method for treating arthritis by delivering to a subject a lentiviral vector encoding any therapeutic gene, wherein the lentiviral vector is administered to the subject via any route of administration (systemic or local). At best the specification teaches that lentiviral-based gene delivery of interleukin-1 receptor antagonist to the arthritic join rat model. Besides the interleukin-1 receptor antagonist the specification as filed fails to provide any evidence that any therapeutic gene (as claimed) is capable of treating arthritis. In addition besides the local administration of a lentiviral vector encoding the IL-1Ra coding sequence, the specification fails to provide any evidence that arthritis can be treated by systemic administration of any such vector.

State Of Art And Predictability

The scope of the instant invention encompasses genetic modification of a cell in-vivo, therefore the invention falls in the realm of gene therapy. The gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy (see Goncalves, Bioessays. 27(5):506-517, 2005; Juengst, BMJ, 326:1410-11, 2003; Check NATURE 422:7, 2003; Couzin et al, SCIENCE 307:1028, 2005; Rosenberg et al, SCIENCE 287:1751, 2000; Anderson, NATURE 392:25-30, 1998; Touchette, NAT. MED. 2(1) 7-8, 1996). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. Furthermore, Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success. The advisory panel further emphasized the need for a greater

understanding of an underlying mechanism that contribute to a genetic disease along with the pathogenesis of the disease.

In instant case the treatment of arthritis is considered highly unpredictable. The arthritis is a crippling disease that commonly is associated with chronic inflammation of the joints. Although considered to be a systemic disorder, the symptoms of rheumatoid arthritis are most prominent in the wrist, knees, proximal interphalangeal and metacarpophalangeal joints. The debilitating effects of the disease occur progressively with time. The synovium, normally a thin layer of tissue that lines the internal surfaces of the joint capsule, becomes dramatically thickened and hypercellular from infiltrating leukocytes and proliferating synovial cells. Chronic secretion of inflammatory cytokines by monocytes and macrophages causes the cells in the synovium to become activated, giving the hypertrophied tissue an aggressive phenotype. The synovium enlarges to a pannus that attaches to, invades, and erodes the articular cartilage and subchondral bone. With time, the cumulative degradation of the joint structures often results in severe disfigurement and loss of function. The exact stimulus that initiates the progression of rheumatoid arthritis is largely unknown. Studies of patients suggest that exposure to specific infectious agents in concert with a genetic predisposition may lead to a higher incidence of disease. Until more is known about the etiology of rheumatoid arthritis, it will remain impossible to design a treatment strategy aimed at the cause of disease. Many pharmacologic agents used in the treatment of patients with rheumatoid arthritis such as nonsteroidal antiinflammatory drugs which largely are used for treatment of painful symptoms, do little to halt disease progression. Disease modifying antirheumatic drugs are slower acting and may act more directly on the underlying disease processes, but in most cases they fail to arrest or reverse the disease. Prolonged use of many of these agents can be associated with side effects such as hypertension, renal and hepatotoxicity, and stomach ulceration (see Boissier et al Rematismo 56-N1(suppl.1)51-61, 2004; Gouze et al Expert Opin. Biol. Ther. 1(6):971-978, 2001). The scope of instant invention encompasses the use any therapeutic gene for the treatment of arthritis associated with any etiology. Besides the using interleukin-1 receptor antagonist, the specification as filed fails to disclose that any other therapeutic

gene is capable of treating the arthritis upon the administration a lentiviral vector encoding the therapeutic gene. Specifically the specification as failed fails to provide any evidence that would enable one of skill to conclude that a lentiviral vector encoding a therapeutic gene selected from *TIMP-1, TIMP-2, TIMP-3, TIMP-4, IL-4, IL-10, IL_11, IL-13 PDGF-AA, PDGF-AB, PDGF-BB, sTNF-R55, sTNF-R75, fibronectin, a fibronectin fragment, Transforming Growth Factor-b (TGF-b), Insulin-Like Growth Factor (IGF), Leukemia Inhibitory Factor (LIF), LIF binding protein (LBP), Bone Mophogenic Protein-2 (BMP-2), Bone Morphogenic Protein-7 (BMP-7), Insulin Growth Factor (IGF)-I, Indian hedgehog (Ihh), parathyroid hormone-related protein (PTHrP), hyaluronan synthase, Sox-9, Superficial Zone Protein, Cartilage Growth and Differentiation Factors (CGDF), Bc1-2, soluble TNF-R75, soluble TNF-R75, or a urokinase plasminogen activator (uPA)*, when delivered to an arthritic patient via any route of administration is capable of treating arthritis associated with any etiology.

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). Although, the gene therapy holds much promise to come, the success will only be achieved through continued rigorous research on the most fundamental mechanisms that contribute to a genetic disease along with the pathogenesis of the disease, gene delivery and gene expression in animals

In instant case gene based therapies to arthritis using any therapeutic gene of interest is not considered routine in the art and without sufficient guidance to a specific therapeutic gene and its substantial role in the modulation of the disease the experimentation left to those skilled in the art is unnecessarily, and improperly,

extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4, 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glorioso et al (US 5,858,355 1999) in view of Ghivizzani et al DDT 6(5), 2001 and Trono Gene Therapy 7:20-23, 2000.

Glorioso teaches retroviral vector encoding interleukin-1 receptor-antagonist mediated gene therapy for the treatment of arthritis. The cited art teaches a method for treating arthritis by administering a viral vector (MFG-IRAP) encoding Interlukin-1-alpha Receptor antagonist Protein (IRAP). The cited art teaches intra-articular injection of MFG-IRAP to synovial cells of an inflamed knee joint in a rabbit model (col.36, example-XV). The cited art further teaches that the expression of IRAP within the joint space results in a reduction of cartilage destruction or reduction in synovitis (col 53-54).

Even though the cited art teaches the use of retroviral vector mediated gene therapy for arthritis, the cited art does not specifically teaches the use of a lentiviral vector (i.e. HIV) for arthritis gene therapy.

Ghivizzani teaches direct gene delivery strategies fro the treatment of rheumatoid arthritis see pages 259-267). In specific reference to Trono (Gene Therapy 7:20-23, 2000) the cited art specifically teaches that lentiviral vectors are the vector of choice,

since these vectors are able to transduce non-mitotic cells and enable the advantage of retroviral-mediated gene transfer to be adapted to direct gene delivery to the joints.

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Glorioso by substituting the retroviral vectors (MFG-IRAP) with a lentiviral vector that encodes IRAP. One would have been motivated to do so to transduce non-mitotic cells via direct gene delivery to the joints. One would have a reasonable expectation of success, since use of the lentiviral vectors to transduce non-mitotic cells via direct gene delivery has been routine in the art at time the instant invention was madeThus the invention as claimed is prima facie obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**

SUMESH KAUSHAL
PRIMARY EXAMINER
ART UNIT 1633